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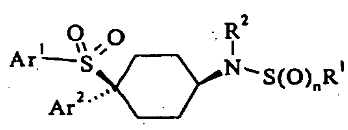

(I)

(57) Abstract: Compounds of formula (I) inhibit the processing of APP by gamma-secretase, and hence are useful in treating or preventing Alzheimer's disease.

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CYCLOHEXYL SULPHONES AS GAMMA-SECRETASE INHIBITORS

The present invention relates to a novel class of compounds, their salts, pharmaceutical compositions comprising them, processes for making them and their use in therapy of the human body. In particular, the invention relates to novel cyclohexyl sulphones which inhibit the processing of APP by γ-secretase, and hence are useful in the treatment or prevention of Alzheimer's disease.

Alzheimer's disease (AD) is the most prevalent form of dementia. Although primarily a disease of the elderly, affecting up to 10% of the population over the age of 65, AD also affects significant numbers of younger patients with a genetic predisposition. It is a neurodegenerative disorder, clinically characterized by progressive loss of memory and cognitive function, and pathologically characterized by the deposition of extracellular proteinaceous plaques in the cortical and associative brain regions of sufferers. These plaques mainly comprise fibrillar aggregates of β-amyloid peptide (Aβ). The role of secretases, including the putative γ-secretase, in the processing of amyloid precursor protein (APP) to form Aβ is well documented in the literature and is reviewed, for example, in WO 01/70677.

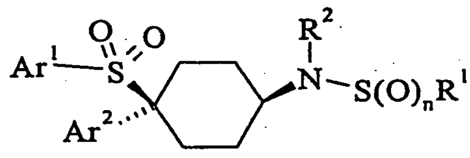
There are relatively few reports in the literature of compounds with inhibitory activity towards γ-secretase, as measured in cell-based assays. These are reviewed in WO 01/70677. Many of the relevant compounds are peptides or peptide derivatives.

WO 00/50391 discloses a broad class of sulphonamides as modulators of the production of β-amyloid, but neither discloses nor suggests the compounds of the present invention.

The present invention provides a novel class of cyclohexyl sulphones which are useful in the treatment or prevention of AD by inhibiting the processing of APP by the putative γ-secretase, thus arresting the production of Aβ. The compounds of the invention generally combine a

high affinity for the target enzyme with favourable pharmacokinetic properties.

According to the invention, there is provided a compound of formula I:



I

wherein n is 1 or 2;

R^1 represents CF_3 or C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-9}cycloalkyl or C_{3-6}cycloalkylC_{1-6}alkyl, any of which may bear up to 2 substituents selected from halogen, CN, CF_3, OR^3, COR^3, CO_2R^3, $OCOR^4$, SO_2R^4, $N(R^5)_2$, and $CON(R^5)_2$,

or R^1 represents aryl, arylC_{1-6}alkyl, C-heterocyclyl or C-heterocyclylC_{1-6}alkyl;

R^2 represents H or C_{1-4}alkyl;

R^3 represents H, C_{1-4}alkyl, phenyl or heteroaryl;

R^4 represents C_{1-4}alkyl, phenyl or heteroaryl;

R^5 represents H or C_{1-4}alkyl, or two R^5 groups together with a nitrogen atom to which they are mutually attached complete an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine or thiomorpholine-1,1-dioxide ring;

Ar^1 and Ar^2 independently represent phenyl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, CHF_2, OH, OCF_3, CHO, CH=NOH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, C_{2-6}acyl, C_{2-6}alkenyl and C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

"aryl" at every occurrence thereof refers to phenyl or heteroaryl which optionally bear up to 3 substituents selected from halogen, CN, NO_2, CF_3, OCF_3, OR^3, COR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$, $CON(R^5)_2$ and

optionally-substituted C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, phenyl, OR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$ and $CON(R^5)_2$; and

"C-heterocyclyl" and "N-heterocyclyl" at every occurrence thereof refer respectively to a heterocyclic ring system bonded through carbon or nitrogen, said ring system being non-aromatic and comprising up to 10 atoms, at least one of which is O, N or S, and optionally bearing up to 3 substituents selected from oxo, halogen, CN, NO_2, CF_3, OCF_3, OR^3, COR^3, CO_2R^3, $OCOR^4$, OSO_2R^4, $N(R^5)_2$, $CON(R^5)_2$ and optionally-substituted phenyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, OR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$ and $CON(R^5)_2$;

or a pharmaceutically acceptable salt thereof.

Where a variable occurs more than once in formula I, the individual occurrences are independent of each other, unless otherwise indicated.

As used herein, the expression "C_{1-x}alkyl" where x is an integer greater than 1 refers to straight-chained and branched alkyl groups wherein the number of constituent carbon atoms is in the range 1 to x. Particular alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C_{2-6}alkenyl", "hydroxyC_{1-6}alkyl", "heteroarylC_{1-6}alkyl", "C_{2-6}alkynyl" and "C_{1-6}alkoxy" are to be construed in an analogous manner.

The expression "C_{3-9}cycloalkyl" as used herein refers to nonaromatic monocyclic or fused bicyclic hydrocarbon ring systems comprising from 3 to 9 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl and bicyclo[2.2.1]heptyl. Monocyclic systems of 3 to 6 members are preferred.

The expression "C_{3-6} cycloalkylC_{1-6}alkyl" as used herein includes cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

The expression "C_{2-6}acyl" as used herein refers to C_{1-5}alkylcarbonyl groups in which the alkyl portion may be straight chain, branched or cyclic, and may be halogenated. Examples include acetyl, propionyl and trifluoroacetyl.

The expression "heterocyclyl" as defined herein includes both monocyclic and fused bicyclic systems of up to 10 ring atoms selected from C, N, O and S. Mono- or bicyclic systems of up to 7 ring atoms are preferred, and monocyclic systems of 4, 5 or 6 ring atoms are most preferred. Examples of heterocyclic ring systems include azetidinyl, pyrrolidinyl, 3-pyrrolinyl, terahydrofuryl, 1,3-dioxolanyl, tetrahydrothiophenyl, tetrahydropyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, 2,5-diazabicyclo[2.2.1]heptyl, 2-aza-5-oxabicyclo[2.2.1]heptyl and 1,4-dioxa-8-azaspiro[4.5]decanyl. Unless otherwise indicated, heterocyclyl groups may be bonded through a ring carbon atom or a ring nitrogen atom where present. "C-heterocyclyl" indicates bonding through carbon, while "N-heterocyclyl" indicates bonding through nitrogen.

The expression "heteroaryl" as used herein means a monocyclic system of 5 or 6 ring atoms, or fused bicyclic system of up to 10 ring atoms, selected from C, N, O and S, wherein at least one of the constituent rings is aromatic and comprises at least one ring atom which is other than carbon. Monocyclic systems of 5 or 6 members are preferred. Examples of heteroaryl groups include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furyl, thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl, triazolyl and thiadiazolyl groups and benzo-fused analogues thereof. Further examples of heteroaryl groups include tetrazole, 1,2,4-triazine and 1,3,5-triazine. Pyridine rings may be in the N-oxide form.

Where a phenyl group or heteroaryl group bears more than one substituent, preferably not more than one of said substituents is other than halogen or alkyl. Where an alkyl group bears more than one

substituent, preferably not more than one of said substituents is other than halogen.

The term “halogen” as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

For use in medicine, the compounds of formula I may advantageously be in the form of pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula I or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, benzenesulfonic acid, methanesulfonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Alternatively, where the compound of the invention carries an acidic moiety, a pharmaceutically acceptable salt may be formed by neutralisation of said acidic moiety with a suitable base. Examples of pharmaceutically acceptable salts thus formed include alkali metal salts such as sodium or potassium salts; ammonium salts; alkaline earth metal salts such as calcium or magnesium salts; and salts formed with suitable organic bases, such as amine salts (including pyridinium salts) and quaternary ammonium salts.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In the compounds of formula I, n is 1 or 2, preferably 2.

R^1 is preferably CF_3, aryl or arylalkyl, or an alkyl, alkenyl, cycloalkyl or cycloalkylalkyl group, optionally substituted as described

previously. Preferred substituents include halogen (especially fluorine or chlorine), CF_3, CN, OR^3 (especially OH, OMe and OEt), COR^3 (especially acetyl), CO_2R^3 (especially CO_2H, CO_2Me and CO_2Et), SO_2R^4 (especially methanesulfonyl), $N(R^5)_2$ (especially when the R^5 groups complete a ring) and $CON(R^5)_2$ (especially $CONH_2$).

Examples of alkyl groups represented by R^1 include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, 2,2,2-trifluoroethyl, chloromethyl, 3-chloropropyl, 2-chloro-2-propyl, cyanomethyl, 2-hydroxyethyl, 2-methoxyethyl, 2-hydroxy-2-methylpropyl, carboxymethyl, methoxycarbonylmethyl, 1-carboxyethyl, 1-ethoxycarbonylethyl, carbamoylmethyl, 2-(pyrrolidin-1-yl)ethyl, 2-(morpholin-4-yl)ethyl and $MeSO_2CH_2$-.

Examples of alkenyl groups represented by R^1 include vinyl and allyl.

Examples of cycloalkyl and cycloalkylalkyl groups represented by R^1 include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl and cyclopentylmethyl.

When R^1 represents aryl or arylalkyl, the aryl group may be phenyl or heteroaryl (especially 5- or 6-membered heteroaryl), optionally substituted as defined previously. Preferred substituents include halogen (especially chlorine, bromine or fluorine), CN, CF_3, OCF_3, alkyl (especially methyl), OH, alkoxy (especially methoxy) and alkoxycarbonyl (such as methoxycarbonyl). Preferred heteroaryl groups include pyridine, pyrimidine, furan, thiophene, thiazole, isothiazole, isoxazole, pyrazole, imidazole, triazole, thiadiazole and tetrazole, especially pyridine, furan, thiophene, thiazole, isothiazole, isoxazole, pyrazole, imidazole, triazole, and tetrazole.

Examples of aryl groups represented by R^1 include phenyl, 2-, 3- and 4-fluorophenyl, 2,4-difluorophenyl, 2-chlorophenyl, 2-bromophenyl, 2-cyanophenyl, 2-methylphenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 5-chloro-2-methoxyphenyl, 2-pyridyl, 4-pyridyl, 6-chloro-3-pyridyl, 2-furyl,

2-thienyl, 3-thienyl, 2-thiazolyl, 5-isothiazolyl, 2-imidazolyl, 2-methylfuran-3-yl, 5-chloro-2-thienyl, 4-chloro-2-thienyl, 3-chloro-2-thienyl, 3-bromo-2-thienyl, 4-bromo-2-thienyl, 5-methyl-2-thienyl, 2-(methoxycarbonyl)-3-thienyl, 4-methylthiazol-3-yl, 1-methylimidazol-2-yl, 1-methylimidazol-5-yl, 1-methylimidazol-4-yl, 3-chloro-1,5-dimethylpyrazol-4-yl, 3,5-dimethylisoxazol-4-yl, 1-methyl-1,2,3,4-tetrazol-5-yl, 1,2,4-triazol-3-yl, 1-methyl-1,2,4-triazol-3-yl, 2-methyl-1,2,4-triazol-3-yl and 4-methyl-1,2,4-triazol-3-yl.

Arylalkyl groups represented by R^1 are typically optionally substituted benzyl, phenethyl, heteroarylmethyl or heteroarylethyl groups. Examples include benzyl, 2-furylmethyl, 2-thienylmethyl and 1-(2-thienyl)ethyl. Preferred examples include benzyl.

R^2 preferably represents H or methyl, most preferably H.

R^3 preferably represents H, C_{1-4}alkyl, phenyl, pyridyl, or 5-membered heteroaryl. Most preferably, R^3 represents H or C_{1-4}alkyl.

R^4 preferably represents C_{1-4}alkyl, phenyl, pyridyl, or 5-membered heteroaryl. Most preferably, R^3 represents C_{1-4}alkyl.

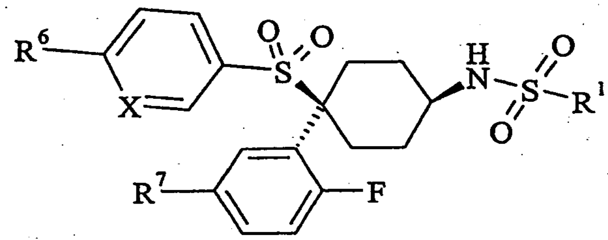
Ar^1 and Ar^2 independently represent optionally substituted phenyl or heteroaryl. Ar^1 is preferably selected from optionally substituted phenyl and optionally substituted 6-membered heteroaryl. Preferred 6-membered heteroaryl embodiments of Ar^1 include optionally substituted pyridyl, in particular optionally substituted 3-pyridyl. Ar^1 is preferably selected from 6-(trifluoromethyl)-3-pyridyl and phenyl which is optionally substituted in the 4-position with halogen, CN, vinyl, allyl, acetyl, methyl or mono-, di- or trifluoromethyl. In one preferred embodiment of the invention Ar^1 represents 4-chlorophenyl. In another preferred embodiment Ar^1 represents 4-trifluoromethylphenyl. In a further preferred embodiment, Ar^1 represents 6-(trifluoromethyl)-3-pyridyl.

Ar^2 preferably represents optionally substituted phenyl, in particular phenyl bearing 2 or 3 substituents selected from halogen, CN, CF_3 and optionally-substituted alkyl. Ar^2 is typically selected from phenyl

groups bearing halogen substituents (preferably fluorine) in the 2- and 5-positions or in the 2-, 3- and 6-positions, or from phenyl groups bearing a fluorine substituent in the 2-position and halogen, CN, methyl or hydroxymethyl in the 5-position. In a preferred embodiment of the invention, Ar^2 represents 2,5-difluorophenyl.

In a particular embodiment, Ar^1 is 6-trifluoromethyl-3-pyridyl, 4-chlorophenyl or 4-trifluoromethylphenyl and Ar^2 is 2,5-difluorophenyl.

A preferred subclass of the compounds of the invention are the compounds of formula II:



II

wherein X represents N or CH;

R^6 represents H, F, Cl, Br, CN, CF_3, $CH{=}CH_2$ or CH_3;

R^7 represents F, Cl, Br, CN, CH_3 or CH_2OH; and

R^1 has the same definition and preferred identities as before;

and pharmaceutically acceptable salts thereof.

When X represents N, R^6 is preferably CF_3.

In a preferred embodiment, R^1 is selected from:

(a) CF_3;

(b) C_{1-6}alkyl which optionally bears up to 2 substituents selected from halogen, CN, CF_3, OR^3, CO_2R^3, SO_2R^4, $N(R^5)_2$, and $CON(R^5)_2$; and

(c) phenyl, pyridyl or 5-membered heteroaryl which optionally bear up to 3 substituents selected from halogen, CN, CF_3, OR^3, COR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$, $CON(R^5)_2$ and optionally-substituted C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, phenyl, OR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$ and $CON(R^5)_2$;

where R^3, R^4 and R^5 have the same definitions and preferred identities as before.

R^1 very aptly represents CF_3.

Examples of individual compounds in accordance with the invention are provided in the Examples section appended hereto.

The compounds of formula I have an activity as modulators of the processing of APP by γ-secretase.

The invention also provides pharmaceutical compositions comprising one or more compounds of formula I or the pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums or surfactants such as sorbitan monooleate, polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 250 mg, for

example 1, 2, 5, 10, 25, 50, 100, 200 or 250 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil or coconut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, poly(vinylpyrrolidone) or gelatin.

The present invention also provides a compound of formula I or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human body. Preferably the treatment is for a condition associated with the deposition of β-amyloid. Preferably the condition is a neurological disease having associated β-amyloid deposition such as Alzheimer's disease.

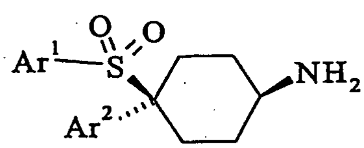
The present invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing Alzheimer's disease.

The present invention further provides a method of treatment of a subject suffering from or prone to a condition associated with the

deposition of β-amyloid which comprises administering to that subject an effective amount of a compound according to formula I or a pharmaceutically acceptable salt thereof. Preferably the condition is a neurological disease having associated β-amyloid deposition such as Alzheimer's disease.

For treating or preventing Alzheimer's Disease, a suitable dosage level is about 0.01 to 250 mg/Kg per day, preferably about 0.10 to 100 mg/Kg per day, especially about 1.0 to 50 mg/Kg, and for example about 10 to 30 mg/Kg of body weight per day. Thus, a dose of about 500mg per person per day may be considered. The compounds may be administered on a regimen of 1 to 4 times per day. In some cases, however, dosage outside these limits may be used.

The compounds of formula I in which R^2 is H may be prepared by reacting a sulfinyl chloride R^1SOCl or a sulfonyl chloride R^1SO_2Cl or a sulfonic anhydride $(R^1SO_2)_2O$ with an amine of formula III:

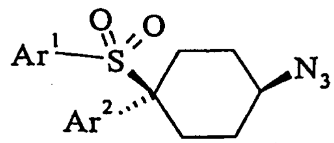


III

where R^1, Ar^1 and Ar^2 have the same meanings as before. The reaction is typically carried out at ambient or reduced temperature in the presence of a tertiary amine such as triethylamine in an aprotic solvent such as dichloromethane.

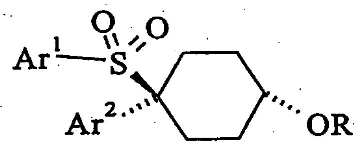
The compounds of formula I in which R^2 is other than H may be prepared by alkylation of the corresponding compounds of formula I in which R^1 is H, e.g. by heating with the appropriate alkyl iodide in THF in the presence of sodium hydride.

The amines of formula III may be obtained by reduction of the azides IV:



IV

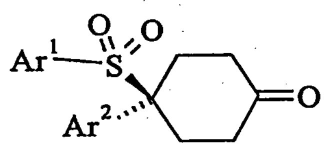
where Ar^1 and Ar^2 have the same meanings as before. The azides IV are obtained via nucleophilic displacement of the mesylates V(a), formed from the *trans* alcohols V(b) by reaction with methanesulfonyl chloride:



V (a) $R = SO_2Me$

(b) $R = H$

where Ar^1 and Ar^2 have the same meanings as before. The alcohols V(b) are obtained by reduction of the cyclohexanones VI:



VI

where Ar^1 and Ar^2 have the same meanings as before. The reduction may be carried out using sodium borohydride in ethanol, with isolation of the *trans* isomer by chromatography.

The synthesis of cyclohexanones VI and their conversion to amines III, is described in WO 02/081435.

It will be apparent to those skilled in the art that individual compounds of formula I prepared by the above routes may be converted into other compounds in accordance with formula I by means of well known synthetic techniques such as alkylation, esterification, amide coupling, hydrolysis, oxidation and reduction. Such techniques may likewise be carried out on precursors of the compounds of formula I. For example, substituents on the aromatic groups Ar^1 or Ar^2 may be added or

interconverted by means of standard synthetic processes carried out on the compounds of formula I or their precursors. For example, a chlorine or bromine atom on Ar^1 or Ar^2 may be replaced by vinyl by treatment with vinyltributyltin in the presence of tri-t-butylphosphine, cesium fluoride and tris(dibenzylideneacetone)dipalladium(0). Ozonolysis of the vinyl group provides the corresponding formyl derivative, which may be transformed in a variety of ways, including oxidation to the corresponding acid, reduction to the corresponding benzyl alcohol, and conversion to the corresponding nitrile by treatment with hydroxylamine then triphenylphosphine and carbon tetrachloride.

Where they are not themselves commercially available, the starting materials and reagents employed in the above-described synthetic schemes may be obtained by the application of standard techniques of organic synthesis to commercially available materials.

It will be appreciated that many of the above-described synthetic schemes may give rise to mixtures of stereoisomers. Such mixtures may be separated by conventional means such as fractional crystallisation and preparative chromatography.

Certain compounds according to the invention may exist as optical isomers due to the presence of one or more chiral centres or because of the overall asymmetry of the molecule. Such compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallisation and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 3rd ed., 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

An assay which can be used to determine the level of activity of compounds of the present invention is described in WO01/70677. A preferred assay to determine such activity is as follows:

1) SH-SY5Y cells stably overexpressing the βAPP C-terminal fragment SPA4CT, are cultured at 50-70% confluency. 10mM sodium butyrate is added 4 hours prior to plating.

2) Cells are plated in 96-well plates at 35,000 cells/well/100μL in Dulbecco's minimal essential medium (DMEM) (phenol red-free) + 10% foetal bovine serum (FBS), 50mM HEPES buffer (pH7.3), 1% glutamine.

3) Make dilutions of the compound plate. Dilute stock solution 18.2x to 5.5% DMSO and 11x final compound concentration. Mix compounds vigorously and store at 4°C until use.

4) Add 10μL compound/well, gently mix and leave for 18h at 37°C, 5% CO_2.

5) Prepare reagents necessary to determine amyloid peptide levels, for example by Homogeneous Time Resolved Fluorescence (HTRF) assay.

6) Plate 160μL aliquots of HTRF reagent mixture to each well of a black 96-well HTRF plate.

7) Transfer 40μL conditioned supernatant from cell plate to HTRF plate. Mix and store at 4°C for 18 hours.

8) To determine if compounds are cytotoxic following compound administration, cell viability is assessed by the use of redox dye reduction. A typical example is a combination of redox dye MTS (Promega) and the

electron coupling reagent PES. This mixture is made up according to the manufacturer's instructions and left at room temperature.

9) Add 10μL/well MTS/PES solution to the cells; mix and leave at 37°C.

10) Read plate when the absorbance values are approximately 0.4 – 0.8. (Mix briefly before reading to disperse the reduced formazan product).

11) Quantitate amyloid beta 40 peptide using an HTRF plate reader.

Alternative assays are described in *Biochemistry*, 2000, 39(30), 8698-8704.

See also, *J. Neuroscience Methods*, 2000, 102, 61-68.

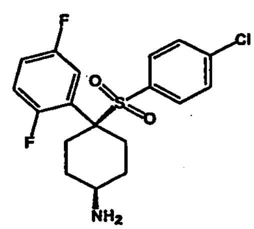
The Examples of the present invention all had an ED_{50} of less than 0.5μM, in most cases less than 100nM, and in preferred cases less than 10nM, in at least one of the above assays.

The following examples illustrate the present invention.

EXAMPLES

Intermediate A

4-(4-chlorobenzenesulfonyl)-4-(2,5-difluorophenyl)cyclohexylamine



(1) 4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanone was prepared as described in WO 02/081435 (Example 2).

This cyclohexanone (0.1 g, 0.26 mmol) in methanol (2 ml) was treated with $NaBH_4$ (0.098 g, 0.26 mmol), stirred for 1 hour, quenched with HCl (1N, 10 ml), diluted with ethyl acetate (20 ml), then the organic phase was separated, dried ($MgSO_4$) and evaporated to dryness. The *trans* 4-[(4-chlorophenyl)sulfonyl]-4-(2, 5-difluorophenyl)cyclohexanol was purified on silica eluting with hexane-ethyl acetate mixtures. 0.052 g. ^{1}H NMR $CDCl_3$ 7.39-7.33 (4H, m), 7.11-7.02 (2H, m), 6.88-6.82 (1H, m), 3.80-3.73 (1H, m),

2.80-2.60 (2H, m), 2.22-2.16 (2H, m), 2.08-2.04 (2H, m), 1.53(1H, br) and 1.27-1.13 (2H, m).

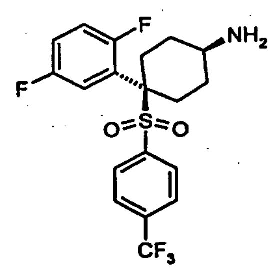
(2) To this alcohol (2.7 g, 6.9 mmol) and triethylamine (1.45 ml, 10.3 mmol) in dichloromethane (50 ml) was added methanesulfonyl chloride (0.645 ml, 8.9 mmol) at -30°C. After 30 minutes the mixture was washed with water (20 ml), 10% aqueous citric acid (20 ml) and saturated aqueous sodium hydrogen carbonate (50 ml), dried ($MgSO_4$) and evaporated to dryness. The solid was triturated with ether to give the mesylate (2.6 g).

(3) The mesylate (1.5 g, 3.2 mmol) in dimethylformamide (5 ml) was treated with sodium azide (315 mg, 4.8 mmol) and heated to 90°C for 6 hrs. The mixture was treated with water (80 ml), and extracted with diethyl ether (3 x 50 ml), dried ($MgSO_4$) and evaporated to dryness. The solid was triturated with ether to give the *cis* azide (1.4 g)

(4) The azide (1 g, 2.55 mmol) in tetrahydrofuran (10 ml) and water (1 ml), was treated with triphenylphosphine (740 mg, 2.8 mmol) at room temperature for 15 mins, water (5 ml) was added and the mixture was heated at reflux for 4 hrs. After cooling to room temperature and passage through SCX Varian Bond Elut™ cartridge, the basic fraction was evaporated to give the primary amine. MS MH+ 386(388).

Intermediate B

4-(2,5-difluorophenyl)-4-(4-trifluoromethylbenzenesulfonyl)cyclohexylamine

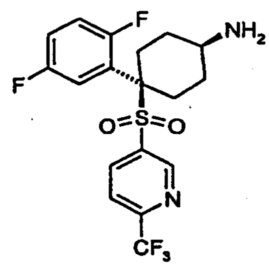


Prepared as for Intermediate A, using the appropriate cyclohexanone (WO 02/081435, Example 41) in step (1), except that the borohydride reduction was carried out at –20°C.

MS (ES+) MH+ 420

Intermediate C

4-(2,5-difluorophenyl)-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-cyclohexylamine



(1) A solution of 3-amino-6-(trifluoromethyl)pyridine (1.62 g, 0.01 mol) in concentrated hydrochloric acid (1.7 mL), was treated with ice (2 g) and cooled to 0°C. Sodium nitrite (0.71 g, 0.01 mol) in water (2 mL) was added slowly, the reaction mixture stirred for 5 minutes at 0°C then treated slowly with a solution of potassium ethyl xanthate (1.92 g, 0.012 mol) in ethanol-water. The reaction mixture was heated at 50-55°C for 30 minutes, cooled and diluted with diethyl ether and water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The resulting xanthate was dissolved in ethanol (30 mL) and treated with potassium hydroxide (3 g) and refluxed (90°C) for 2 h. After cooling and filtering, the filtrate was acidified with citric acid and diluted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography on silica gave the (trifluoromethyl)pyridinethiol as a yellow oil (0.79 g, 44%).
^1H NMR (360 MHz, $CDCl_3$) δ 8.57 (1H, d, J = 2.0 Hz), 7.74 (1H, dd, J = 8.1, 2.0 Hz), 7.54 (1H, d, J = 8.1 Hz), 3.62 (1H, s).

(2) This thiol (0.5 g, 2.8 mmol) was reacted first with 2,5-difluorobenzyl bromide and subsequently with 3-chloroperoxybenzoic acid by the procedure described for Intermediate 1 in WO 02/081435 to gave the pyridyl benzyl sulfone as a white powder (0.82 g, 87% over 2 steps).

^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (1H, d, J = 2.1 Hz), 8.18 (1H, dd, J =8.1, 2.1 Hz), 7.80 (1H, d, J = 8.1 Hz), 7.21-7.17 (1H, m), 7.10-7.04 (1H, m), 6.93-6.88 (1H, m), 4.46 (2H, s).

(3) This sulfone (50 mg, 0.15 mmol) in tetrahydrofuran (5 mL) at 0°C was treated with potassium *tert*-butoxide (17 mg, 0.15 mmol), then with 2,2-bis(2-iodoethyl)-1,3-dioxolane (H. Niwa et al, J. Am. Chem. Soc., 1990, 112, 9001) (86 mg, 0.23 mmol), stirred for 1 h at room temperature and then for 1 h at 70°C. The cooled reaction mixture was treated with more potassium *tert*-butoxide (1.2 equivalents) and 2,2-bis(2-iodoethyl)-1,3-dioxolane (0.3 equivalents). After heating at 70°C for 1h, then cooling to room temperature, the reaction mixture was diluted with diethyl ether and water, the layers separated and the organic layer washed with water and brine, dried ($MgSO_4$) and evaporated *in vacuo.* Purification by column chromatography on silica gave the desired cyclohexanone cyclic ketal (38 mg, 56%) as a white solid.

^1H NMR (360 MHz, $CDCl_3$) δ 8.68 (1H, d, J = 2.0 Hz), 7.92 (1H, dd, J = 2.0, 8.1 Hz), 7.73 (1H, d, J = 8.1 Hz), 7.19–7.07 (2H, m), 6.90-6.82 (1H, m), 3.99-3.88 (4H, m), 2.7 (2H, vbrm), 2.5 (2H, vbrappt), 1.85 (2H, brappd), 1.54-1.26 (2H, m).

(4) This ketal (30 mg, 0.065 mmol) was heated at 50°C overnight with *p*-toluenesulfonic acid (15 mg) in 80% acetic acid-water. The reaction mixture was partitioned between diethyl ether and water and the organic layer washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried ($MgSO_4$) and evaporated *in vacuo.* Purification by column chromatography on silica gave the cyclohexanone (25 mg, 92%) as a white solid.

^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (1H, d, J = 2.0 Hz), 7.97 (1H, dd, J = 8.1, 2.0 Hz), 7.77 (1H, d, J = 8.1 Hz), 7.28-7.16 (2H, m), 6.99-6.90 (1H, m), 3.01-2.97 (2H, m), 2.68-2.57 (4H, m), 2.26-2.17 (2H, m).

(5) The cyclohexanone was converted to the title amine by the procedure of Intermediate A, except that the borohydride reduction was carried out at –78°C. M/Z 421 (MH^+).

Sulfonyl Chlorides

The sulfonyl chlorides used in these examples were typically commercially available, or available by literature routes. Representative syntheses include the following:

2-methyl-1-propanesulfonyl chloride

To 2-methyl-1-propanethiol (200 mg, 2.22 mmol) at 0°C in acetonitrile under nitrogen was added KNO_3 (561 mg, 5.5 mmol) then sulfuryl chloride (0.45 ml, 5.5 mmol). The reaction mixture was stirred at 0°C for 3h, diluted with $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give the sulfonyl chloride (293 mg, 95%)

2-chlorosulfonyl-1-methylimidazole

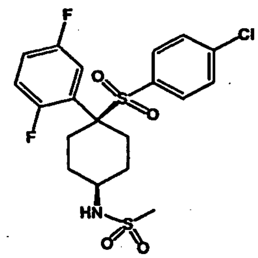
Bleach (12% w/w aq, 110 ml) was cautiously added dropwise to a solution of 2-mercapto-1-methylimidazole (2.0 g) in conc. H_2SO_4 (50 ml) cooled to 0°C. After stirring 30 minutes at 0°C the mixture was diluted with H_2O (30 ml) and dichloromethane (30 ml). The aqueous layer was re-extracted with dichloromethane and the combined organic layers dried ($MgSO_4$) and evaporated to give the product as an oil (730 mg).

5-chlorosulfonyl-1-methyltetrazole

Cl_2(g) was bubbled through a solution of 5-mercapto-1-methyltetrazole (1.518 g) in 2N HCl (25 ml) at 0°C. After 15 minutes the solid precipitate (880mg) was filtered off and washed with H_2O.

Example 1

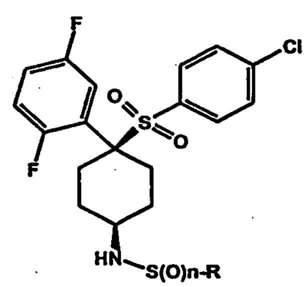
methanesulfonic acid, N-[4-(4-chlorobenzenesulfonyl)-4-(2,5-difluorophenyl)-cyclohexyl]-amide



Methanesulfonyl chloride (24 μL, 0.31 mmol) was added to a solution of Intermediate A (100 mg, 0.28 mmol) and triethylamine (77 μL, 0.56 mmol) in dichloromethane (1.5 ml) at 0°C. After stirring at ambient temperature for 12 hours, the reaction was partitioned between water (50 ml) and dichloromethane (50 ml), the phases separated and the aqueous layer washed twice more with dichloromethane. The combined organic layers were washed with 1N HCl. the acidic layer extracted twice with dichloromethane and the combined organics dried over K_2CO_3 and concentrated. Flash column chromatography eluting with 60/40 hexane / ethyl acetate afforded the title compound (88.5 mg).

MS(ES$^-$) [M-H] 462, 464.

The following examples were prepared by the same procedure, using the appropriate sulfonyl or sulfinyl chloride:



Example	n	R	MS (ES$^-$ (MH$^-$) unless otherwise stated)

Example	n	R	MS (ES$^-$ (MH$^-$) unless otherwise stated)
2	2	CH_2CF_3	530, 532
3	2	^nPr	490, 492
4	2	benzyl	538, 540
5	2	phenyl	524, 526
6	2	2-thienyl	530, 532
7	2	ethyl	476, 478
8	2	5-chloro-2-thienyl	566, 568 $(M+H)^+$
9	2	n-butyl	504, 506
10	2	2-fluorophenyl	542, 544
11	2	3-fluorophenyl	542, 544
12	2	4-fluorophenyl	542, 544
13	2	2-pyridyl	525, 527
14	2	5-methyl-2-thienyl	546, 548 $(MH)^+$
15	2	5-isothiazolyl	531, 533
16	2	4-chloro-2-thienyl	564, 566, 568
17	2	2-(trifluoromethyl)phenyl	616/618$[M+Na]^+$.
18	2	$CH_2CH(CH_3)_2$	506, 508$[MH]^+$
19	2	CH_2SO_2Me	542, 544$[MH]^+$
20	2	2-methylphenyl	540, 542$[MH]^+$
21	2	4-Me-1,2,4-triazol-3-yl	529, 531
22	2	2-thiazolyl	531, 533
23	2	chloromethyl	494, 496, 498
24	2	2-furyl	514, 516
25	2	2-chlorophenyl	558, 560
26	2	2-cyanophenyl	549, 551
27	2	3,5-di-Me-isoxazol-4-yl	543, 545
28	2	3-thienyl	530, 532

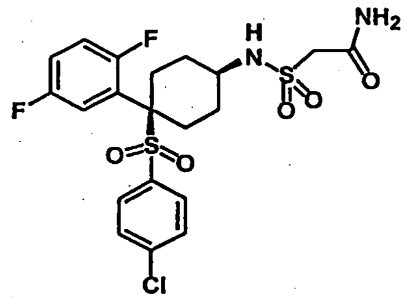
Example	n	R	MS (ES⁻ (MH⁻) unless otherwise stated)
29	2	3-chloropropyl	524, 526
30	2	1-Me-tetrazol-5-yl	532 ,543[MH]$^+$
31	2	1,2,4-triazol-3-yl	517, 519[MH]$^+$
32	2	3-chloro-2-thienyl	564, 566
33	2	1-Me-imidazol-5-yl	530, 532[MH]$^+$
34	2	1-Me-imidazol-4-yl	530, 532[MH]$^+$
35	2	1-Me-imidazol-2-yl	528, 530
36	2	2-bromophenyl	430 [MH-4-Cl-PhSO$_2$]$^+$
37	2	3-Cl-1,5-di-Me-pyrazol-3-yl	-
38	2	CH_2CO_2Me	520, 522
39	1*	Me	272[M-ArSO$_2^-$]$^+$, 448[MH]$^+$, 470[M+Na]$^+$
40	2	3-bromo-2-thienyl	610, 612
41	2	4-bromo-2-thienyl	610, 612
42**	2	2-methoxy-5-chlorophenyl	588, 590
43**	2	2-methoxyphenyl	554, 556

* - MeSOCl – Corey et al *J. Am. Chem. Soc.*, 90, 5548-52 (968).

** - obtained as a 1:1 mixture, separated by chromatography, using the sulfonyl chlorides obtained from treating 2-methoxybenzenethiol with sulfuryl chloride.

Example 44

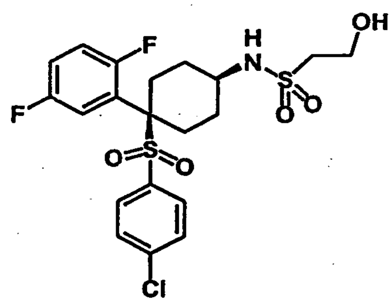
[4-(4-Chlorobenzenesulfonyl)-4-(2,5-difluorophenyl)cyclohexyl]aminosulfonyl-acetamide



Prepared from the ester of Example 38 by treatment with NH_3 (25% aqueous solution) in ethanol. m/z(ES-) = 505/507.

Example 45

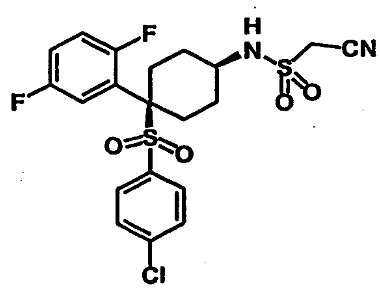
2-hydroxyethanesulfonic acid, N-[4-(4-chlorobenzenesulfonyl)-4-(2,5-difluorophenyl)-cyclohexyl]-amide



Prepared from the ester of Example 38 by reduction with $LiAlH_4$ in tetrahydrofuran. m/z(ES-) = 492/494.

Example 46

cyanomethanesulfonic acid, N-[4-(4-chlorobenzenesulfonyl)-4-(2,5-difluorophenyl)-cyclohexyl]-amide

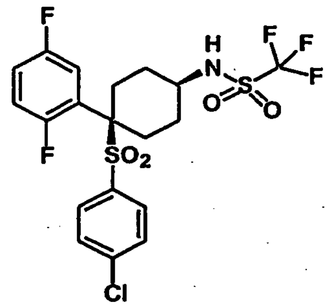


Prepared from the amide of Example 44 by treatment with thionyl chloride and a catalytic amount of dimethylformamide in toluene.

m/z(ES-) = 487/489

Example 47

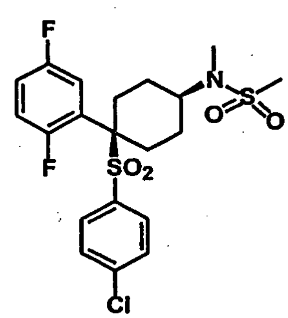
trifluoromethanesulfonic acid, N-[4-(4-chlorobenzenesulfonyl)-4-(2,5-difluorophenyl)-cyclohexyl]-amide



Intermediate A (110 mg, 0.29 mmol) in dichloromethane (3 ml) cooled to 0°C was treated with triethylamine (99 μL, 0.43 mmol) followed by triflic anhydride (117μL, 0.71 mmol). The reaction was stirred at 0°C for 2.5 hours, slowly warming to ambient temperature, then diluted with ethyl acetate, washed with 2N sodium hydroxide, dried ($MgSO_4$) and evaporated to an orange oil which was purified by chromatography 15% ethyl acetate / hexane to yield a white solid (16 mg). ^1H NMR (360MHz, $CDCl_3$) δ 7.39-7.30 (4H, m), 7.09-7.04 (2H, m) 6.88-6.81 (1H, m), 5.86-5.84 (1H, m), 3.82-3.80 (1H, m), 2.64-2.42 (4H, m), 2.07-2.02 (2H, m), 1.66-1.59 (2H, m). m/z = 540, 542[M + Na]$^+$

Example 48

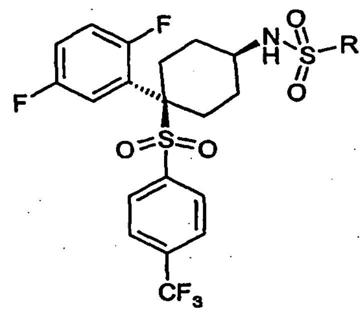
methanesulfonic acid, N-[4-(4-chlorobenzenesulfonyl)-4-(2,5-difluorophenyl)-cyclohexyl]-N-methyl-amide



Prepared from the product of Example 1 by treatment with NaH and MeI in tetrahydrofuran. m/z = 500, 502 $[MNa]^+$

Examples 49-61, 68

The following examples were prepared similarly to Example 1, substituting Intermediate B for Intermediate A and using the appropriate sulfonyl chloride:

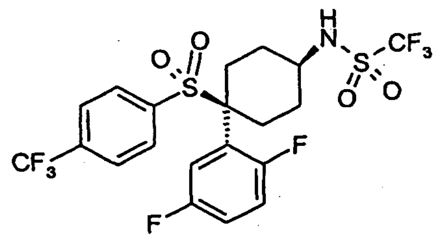


Example	R	MS (MH+) unless otherwise stated
49	Me	499
50	2-furyl	$[MNa^+]$ 572
51	ethyl	$[MH^-]$ 513
52	CH_2SO_2Me	$[MNa^+]$ 598
53	1-Me-imidazol-4-yl	564
54	5-isothiazolyl	567
55	2-pyridyl	$[MNa^+]$ 583, 561
56	5-chloro-2-thienyl	600, 602
57	n-propyl	526
58	2-thienyl	566.
59	6-chloro-3-pyridyl	596, 598
60	3-thienyl	566
61*	vinyl	510, $[MH-SO_2Ar^+]$ 300
68	$2-MeCO_2-3$-thienyl	-

* - prepared using 2-chloroethanesulfonyl chloride

Example 62

trifluoromethanesulfonic acid, N-[4-(2,5-difluorophenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-amide

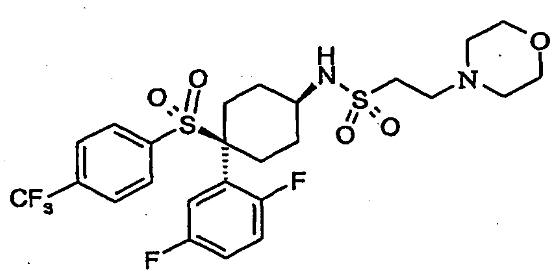


Intermediate B (170 mg, 0.41 mmol) in dry dichloromethane (5 ml) under nitrogen was treated at 0°C with triethylamine (80 μl, 0.62 mmol) and triflic anhydride (133 μl, 0.82 mmol). The reaction was allowed to warm to room temperature, stirred for 3 h. diluted with dichloromethane, washed with water, brine, dried ($MgSO_4$) filtered and evaporated. The residue was purified by flash chromatography eluting with *iso*-hexane/ethyl acetate (1:1) to give a white solid (60 mg).

^{1}H NMR δ (ppm) (DMSO): 1.46-1.53 (2H, m), 1.81 (1H, s), 1.84 (1H, s), 2.41 (2H, t, J = 13.1 Hz), 2.56-2.59 (1H, m), 2.59 (1H, d, J = 2.7 Hz), 3.64 (1H, s), 7.10-7.23 (2H, m), 7.30-7.36 (1H, m), 7.60 (2H, d, J = 8.2 Hz), 7.94 (2H, d, J = 7.6 Hz), 9.77 (1H, d, J = 7.6 Hz).

Example 63

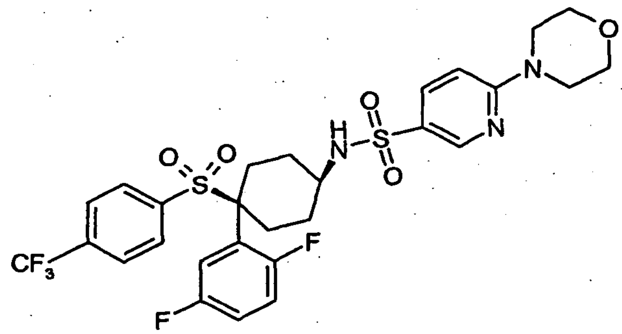
2-(morpholin-4-yl)ethanesulfonic acid, N-[4-(2,5-difluorophenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-amide



Prepared from Example 61 by reaction with excess morpholine in dry dimethylformamide. MS [MH+] 597

Example 64

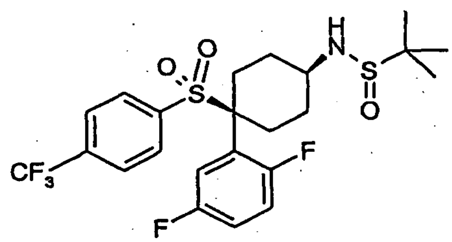
6-(morpholin-4-yl)pyridine-3-sulfonic acid, N-[4-(2,5-difluorophenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-amide



Prepared from example 59 by refluxing in ethanol with morpholine.

Example 65

1,1-dimethylethanesulfinic acid, N-[4-(2,5-difluorophenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-amide

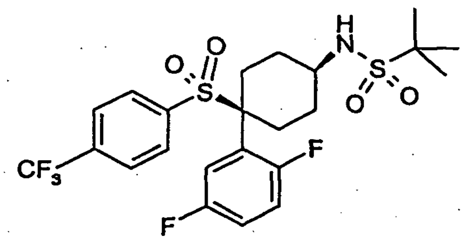


Intermediate B (0.73 g, 1.75 mmol) and 1,1-dimethylethyl sulfinamide (0.21g, 1.75 mmol) in tetrahydrofuran (20 ml) were treated with titanium (IV) ethoxide (0.36 ml, 1.75 mmol) and heated to 80°C for 18 hours. The reaction was quenched with water (0.35 ml) and stirred for 10 minutes before filtering through Celite™. The sulfinimine was cooled to –30°C and treated with L-Selectride ™ (1.75 ml, 1.0 mmol solution), and stirred for 2 hours whilst warming to –5°C. The reaction was then quenched with methanol (2 ml), and partitioned between ethyl acetate (50 ml) and brine (50 ml), dried (MgSO4) and evaporated to dryness. The product was

purified by silica gel chromatography eluting with ethyl acetate/ hexane mixtures. Yield 120 mg. MS MH = 524.

Example 66

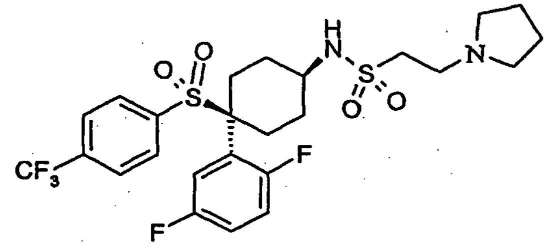
1,1-dimethylethanesulfonic acid, N-[4-(2,5-difluorophenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-amide



Prepared from the product from Example 65 by oxidation with m-chloroperoxybenzoic acid in dichloromethane. MS MH = 540.

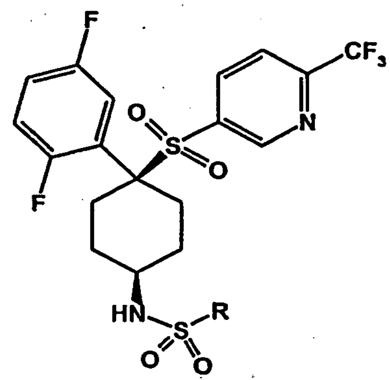
Example 67

2-(pyrrolidin-1-yl)ethanesulfonic acid, N-[4-(2,5-difluorophenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-amide



Prepared as in Example 63, substituting pyrrolidine for morpholine. MS [MH^+] 581

Examples 69-73



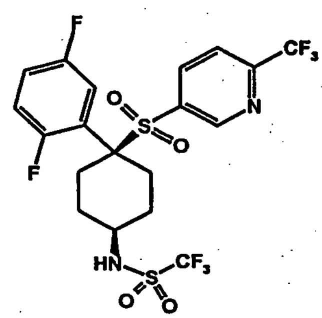
The following sulfonamides were prepared by the procedure of Example 1 using Intermediate C and the appropriate sulfonyl chloride.

Example	R	MS (MH^+)
69	methyl	499
70	2-thienyl	567
71	5-isothiazolyl	568
72	n-propyl	527
73*	2-chloro-2-propyl	561, 563

*Isopropylsulfonyl chloride was used.

Example 74

trifluoromethanesulfonic acid, N-[4-(2,5-difluorophenyl)-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-cyclohexyl]-amide

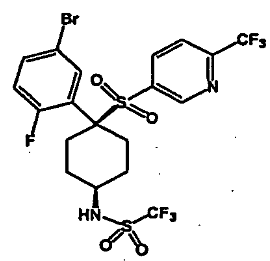


Intermediate C (100 mg) in dichloromethane (5 ml) and treated with triethylamine (1 equivalent) and cooled to -78 °C. Trifluoromethanesulfonic anhydride (2 equivalents) was added, the reaction mixture warmed to -40 °C and stirred at this temperature for 3 h. The mixture was quenched with aqueous citric acid, diluted with ethyl

acetate and warmed to room temperature. The organic phase was separated, washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuo. Purification by column chromatography (eluting with 5/1 hexane/ethyl acetate) gave the title compound (120 mg, 91%) as a white powder. ^1H NMR ($CDCl_3$, 400 MHz) 8.60 (1H, d, J = 1.9), 7.91 (1H, dd, J = 8.2, 1.9), 7.74 (1H, d, J = 8.2), 7.26-7.10 (2H, m), 6.88-6.81 (1H, m), 5.70 (1H, brd, J = 5), 3.83 (1H, brs), 2.64-2.48 (4H, m), 2.11-2.07 (2H, m), 1.70-1.65 (2H, m).

Example 75

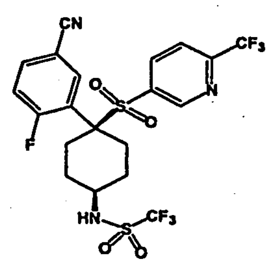
trifluoromethanesulfonic acid, N-[4-(5-bromo-2-fluorophenyl)-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-cyclohexyl]-amide



Prepared by the procedures of Intermediate C (using 2-fluoro-5-bromobenzyl bromide in Step 2) and Example 1 (using trifluoromethanesulfonyl chloride). M/Z = 613, 615 (MH^+).

Example 76

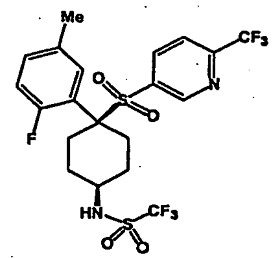
trifluoromethanesulfonic acid, N-[4-(5-cyano-2-fluorophenyl)-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-cyclohexyl]-amide



Prepared from Example 75 (45 mg) by heating with copper cyanide (4 equivalents), pyridine (1 drop) in dimethylformamide at 180°C overnight. M/Z = 559 (MH^+).

Example 77

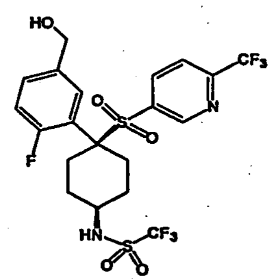
trifluoromethanesulfonic acid, N-[4-(2-fluoro-5-methyl-phenyl)-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-cyclohexyl]-amide



Prepared from Example 75 by treatment with cesium fluoride (2.2 equivalents), tri-tert-butylphosphine (12 mol%), tetramethyltin (2 equivalents), and $Pd_2(dba)_3$ (3 mol%) at 100°C in dioxan for 3 h M/Z = 549 (MH^+).

Example 78

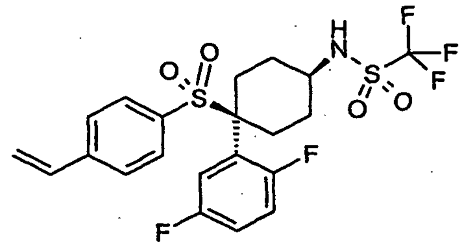
trifluoromethanesulfonic acid, N-[4-(2-fluoro-5-(hydroxymethyl)-phenyl)-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-cyclohexyl]-amide



Prepared from Example 75 by (i) treatment with CsF (2.2 equivalents), tri-tert-butylphosphine (12 mol%), tributylvinyltin (2 equivalents), and $Pd_2(dba)_3$ (3 mol%) in dioxan at 100°C for 2 h.; (ii) treatment of the resulting styrene with ozone at –78°C in dichloromethane/methanol; and (iii) reduction of the resulting aldehyde at –78°C with sodium borohydride (2 equivalents) in ethanol. M/Z = 547 (M-OH+H^+).

Example 79

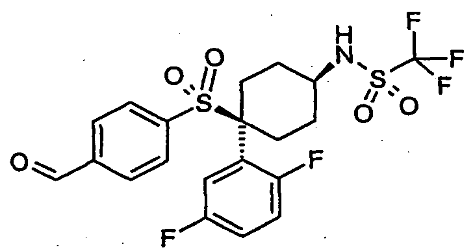
trifluoromethanesulfonic acid, N-[4-(2,5-difluorophenyl)-4-(4-vinylbenzenesulfonyl)-cyclohexyl]-amide



Prepared from Example 47 by treatment with tri-*t*-butylphosphine, cesium fluoride, $Pd_2(dba)_3$ and tributyl(vinyl)tin in dioxan at 100°C for 2 hours.

Example 80

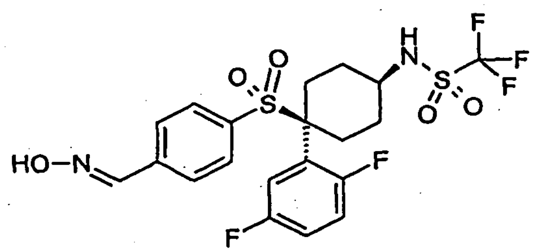
trifluoromethanesulfonic acid, N-[4-(2,5-difluorophenyl)-4-(4-formylbenzenesulfonyl)-cyclohexyl]-amide



Prepared from Example 79 by treatment with ozone in dichloromethane / methanol at –78°C.

Example 81

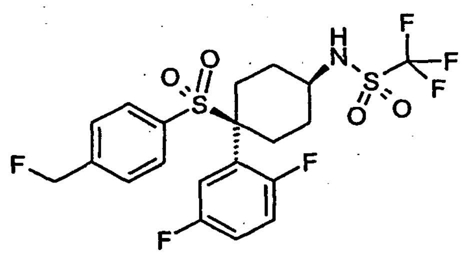
4-{1-(2,5-difluorophenyl)-4-[(trifluoromethanesulfonyl)amino]-cyclohexanesulfonyl}-benzaldehyde oxime



Prepared from Example 80 by treatment with hydroxylamine hydrochloride and sodium acetate in refluxing ethanol.

Example 82

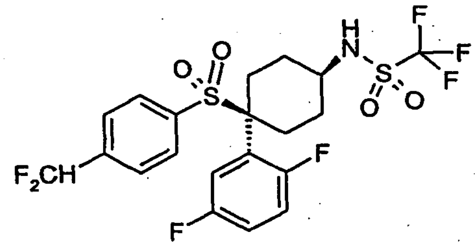
trifluoromethanesulfonic acid, N-[4-(2,5-difluorophenyl)-4-(4-(fluoromethyl)benzenesulfonyl)-cyclohexyl]-amide



Prepared from Example 80 by (i) reduction with sodium borohydride in dry tetrahydrofuran at 0 °C; and (ii) treatment of the resulting benzyl alcohol with diethylaminosulfur trifluoride in dry dichloromethane at−78 °C.

Example 83

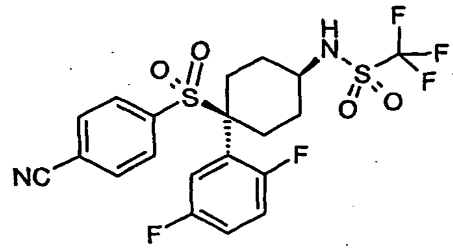
trifluoromethanesulfonic acid, N-[4-(2,5-difluorophenyl)-4-(4-(difluoromethyl)benzenesulfonyl)-cyclohexyl]-amide



Prepared from Example 80 by treatment with diethylaminosulfur trifluoride in dry dichloromethane at room temperature.

Example 84

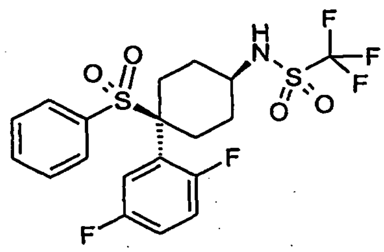
trifluoromethanesulfonic acid, N-[4-(4-cyanobenzenesulfonyl)-4-(2,5-difluorophenyl)-cyclohexyl]-amide



Prepared from Example 81 by treatment with triphenyl phosphine and carbon tetrachloride in acetonitrile.

Example 85

trifluoromethanesulfonic acid, N-[4-(benzenesulfonyl)-4-(2,5-difluorophenyl)-cyclohexyl]-amide



Prepared from Example 47 by hydrogenation over 10% palladium on carbon.

CLAIMS:

1. A compound of formula I:

I

wherein n is 1 or 2;

R^1 represents CF_3 or C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-9}cycloalkyl or C_{3-6}cycloalkylC_{1-6}alkyl, any of which may bear up to 2 substituents selected from halogen, CN, CF_3, OR^3, COR^3, CO_2R^3, $OCOR^4$, SO_2R^4, $N(R^5)_2$, and $CON(R^5)_2$,

or R^1 represents aryl, arylC_{1-6}alkyl, C-heterocyclyl or C-heterocyclylC_{1-6}alkyl;

R^2 represents H or C_{1-4}alkyl;

R^3 represents H, C_{1-4}alkyl, phenyl or heteroaryl;

R^4 represents C_{1-4}alkyl, phenyl or heteroaryl;

R^5 represents H or C_{1-4}alkyl, or two R^5 groups together with a nitrogen atom to which they are mutually attached complete an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine or thiomorpholine-1,1-dioxide ring;

Ar^1 and Ar^2 independently represent phenyl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, CHF_2, OH, OCF_3, CHO, CH=NOH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, C_{2-6}acyl, C_{2-6}alkenyl and C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

"aryl" at every occurrence thereof refers to phenyl or heteroaryl which optionally bear up to 3 substituents selected from halogen, CN, NO_2, CF_3, OCF_3, OR^3, COR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$, $CON(R^5)_2$ and

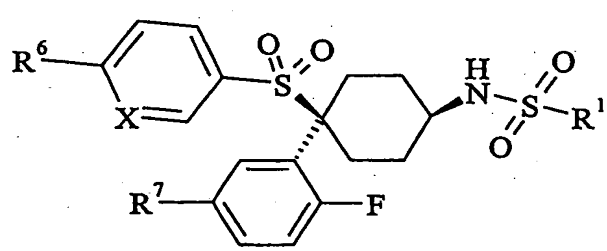
optionally-substituted C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, phenyl, OR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$ and $CON(R^5)_2$; and

"C-heterocyclyl" and "N-heterocyclyl" at every occurrence thereof refer respectively to a heterocyclic ring system bonded through carbon or nitrogen, said ring system being non-aromatic and comprising up to 10 atoms, at least one of which is O, N or S, and optionally bearing up to 3 substituents selected from oxo, halogen, CN, NO_2, CF_3, OCF_3, OR^3, COR^3, CO_2R^3, $OCOR^4$, OSO_2R^4, $N(R^5)_2$, $CON(R^5)_2$ and optionally-substituted phenyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, OR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$ and $CON(R^5)_2$;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein Ar^1 is 6-trifluoromethyl-3-pyridyl, 4-chlorophenyl or 4-trifluoromethylphenyl and Ar^2 is 2,5-difluorophenyl.

3. A compound according to claim 1 of formula II:



II

wherein X represents N or CH;

R^6 represents H, F, Cl, Br, CN, CF_3, $CH=CH_2$ or CH_3;

R^7 represents F, Cl, Br, CN, CH_3 or CH_2OH; and

R^1 is as defined in claim 1;

or a pharmaceutically acceptable salt thereof.

4. A compound according to any previous claim wherein R^1 is CF_3.

5. The compound according to claim 4 which is trifluoromethanesulfonic acid, N-[4-(2,5-difluorophenyl)-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-cyclohexyl]-amide or a pharmaceutically acceptable salt thereof.

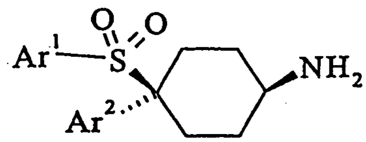
6. A pharmaceutical composition comprising a compound according to any previous claim or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

7. A compound according to any of claims 1-5 or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human body.

8. The use of a compound according to any of claims 1-5 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing Alzheimer's disease.

9. A method of treatment of a subject suffering from or prone to a condition associated with the deposition of β-amyloid which comprises administering to that subject an effective amount of a compound according to any of claims 1-5 or a pharmaceutically acceptable salt thereof.

10. A process for preparing a compound according to claim 1 in which R^2 is H comprising reaction of a sulfinylchloride R^1SOCl or a sulfonyl chloride R^1SO_2Cl or a sulfonic anhydride $(R^1SO_2)_2O$ with an amine of formula III:



III

wherein R^1, Ar^1 and Ar^2 are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

Internatio[illegible] [illegible]cation No
PCT/GB 03/04196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C317/30 C07D213/71 C07D295/10 C07D207/04 A61K31/10
A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 70677 A (MERCK FROSST CANADA INC ;BELANGER PATRICE CHARLES (CA); COLLINS IA) 27 September 2001 (2001-09-27) cited in the application the whole document	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 January 2004	03/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, G

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/04196

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internatic cation No
PCT/GB 03/04196

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0170677	A	27-09-2001	AU	4086101 A	03-10-2001
			CA	2404125 A1	27-09-2001
			EP	1268412 A1	02-01-2003
			WO	0170677 A1	27-09-2001
			JP	2003528076 T	24-09-2003
			AU	1074702 A	15-05-2002
			CA	2427206 A1	10-05-2002
			EP	1334085 A1	13-08-2003
			WO	0236555 A1	10-05-2002